IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: Zuckermann *et al.*	EXAMINER: Wessendorf, T.
SERIAL NO.: 10/025,423	ART UNIT: 1639
FILED: December 18, 2001	Confirmation No. 6469
FOR: **OLIGONUCLEOTIDE TRANSFECTION SCREENING METHOD**	

Appeal Brief

Mail Stop Appeal Brief - Patents
Commissioner of Patents and Trademarks
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This is an appeal to the Board of Appeals and Interferences from the decision of Examiner T. Wessendorf mailed September 23, 2003 and in view of the Advisory Action mailed June 4, 2004, in which pending claims 13-17, 21, and 24-29 stand in final rejection.

Appellants filed a Notice of Appeal on February 23, 2004. The present paper is Appellants' Appeal Brief submitted in compliance with 37 C.F.R. §1.192.

Enclosed herewith are a Petition for a two-month extension of time and a check including the fee of $420. Additionally, enclosed is the fee for filing this appeal brief in the amount of $330. The Commissioner is hereby authorized and requested to charge any deficiency in fees herein to Deposit Account No. 50-2207.

REAL PARTY IN INTEREST

The real party in interest in this application is Chiron Corporation.

RELATED APPEALS AND INTERFERENCES

Appellants are not aware of other appeals or interferences which would directly affect or be directly affected by or have a bearing on the Board's decision in the present appeal.

STATUS OF THE CLAIMS

The application was filed on December 18, 2001 with 30 claims. In a response to requirement for restriction and election of species, filed by the Appellants on January 14, 2003, claims 1-12, 18-20, and 30-32 were canceled with traverse and without prejudice, leaving claims 13-17 and 21-29 pending. In a response to Office Action filed June 26, 2003, claims 13, 15, 21 and 29 were amended for clarity, and claims 22-23 were cancelled. No amendments were made in the response filed by the Appellants on February 23, 2004. The appealed claims in their current status are presented in the Appendix.

STATUS OF AMENDMENTS

All amendments submitted to date have been considered and entered by the Examiner.

SUMMARY OF THE INVENTION

The invention of independent claim 13 provides a method of identifying peptoids, in a library of different-sequence peptoids, which are effective in transfecting a cell with an oligonucleotide. The method comprises:

(i) contacting each peptoid in the library with an oligonucleotide, to form a plurality of peptoid-oligonucleotide mixtures,

(ii) contacting each said mixture with a cell;

(iii) screening each cell for transfection of the oligonucleotide, to identify transfected cells; and

(iv) identifying transfecting peptoids in mixtures contacted with transfected cells.

Exemplary different-sequence peptoids, which comprise a peptoid moiety attached to a lipid moiety, are recited in dependent claim 24 and its dependent claims.

Support for the claims on appeal is found in the specification at, for example, page 5, line 30 to page 8, line 18.

ISSUES

The issues on appeal are:

1. Whether claims 13-15, 21, 24-25 and 27-29 are unpatentable under 35 U.S.C. §102(b) as

being anticipated by Murphy *et al.*, *Proc. Natl. Acad. Sci. USA* **95**:1517 (1998) ("Murphy").

2. Whether claims 13-17, 21, and 24-29 are unpatentable under 35 U.S.C. §103(a) over Murphy *et al.*, *Proc. Natl. Acad. Sci. USA* **95**:1517 (1998), in view of Fasbender *et al.*, U.S. Patent No. 5,935,936 ("Fasbender").

GROUPING OF CLAIMS

With regard to all issues in this Appeal, claims 13-17, 21 and 24-27 stand or fall together.

SUMMARY OF APPELLANTS' ARGUMENTS

Regarding the rejections under 35 U.S.C. §102(b), Appellants assert that the standard for anticipation has not been met, because nowhere does Murphy teach the claimed feature of "contacting each peptoid in the library with an oligonucleotide".

Regarding the rejections under 35 U.S.C. §103(a), Appellants assert that the standard for obviousness has not been met, for the following reasons:

(1) Fasbender teaches away from the use of cationic amphiphiles as carriers for therapeutic molecules, in the absence of a co-lipid as described in Fasbender. Accordingly, one would not be motivated to combine the teachings of this reference with those of Murphy, which employs cationic amphiphilic molecules for transfection of plasmid DNA.

(2) Even if the references were to be combined, the combined teachings would not suggest the current invention. The combined teachings would more likely suggest the use of a cationic amphiphilic molecule as disclosed in Murphy, in combination with a co-lipid as disclosed in Fasbender, for delivery of polynucleotides.

ANALYSIS OF THE REJECTIONS UNDER 35 U.S.C. §102(b)

Claims 13-15, 21, 24-25 and 27-29 stand rejected under 35 U.S.C. §102(b) as being anticipated by Murphy *et al.*, *Proc. Natl. Acad. Sci. USA* **95**:1517 (1998) ("Murphy").

1. The Examiner's Position

In characterizing the Murphy reference, the Examiner states that "[T]he peptoids [in a peptoid library] is then complexed with DNA" and that the complexes are then screened for transfection of cells (Final Office action, dated September 23, 2003, page 6). The Examiner

thereby concludes that the steps of independent claim 13 are shown by the reference.

2. The Reference Teaching

Murphy *et al.* describes identification of cationic peptoids which are effective in the delivery of *plasmid DNA*. The specific plasmid shown is designated pCMV-km-LUC; see "Plasmids and Cell Lines" on page 1518 of the reference. The pCMV-km-LUC plasmid is described in U.S. Patent No. 6,468,986, enclosed herewith, by the same authors. According to Example 5 of the 6,468,986 patent, the plasmid has *over 4,000 basepairs*. See e.g. column 43, lines 19-29 of the '986 patent: "The plasmid used in these experiments, pCMVkmLUC, was constructed by inserting the luc+gene from pSP-luc+ ...into the expression vector pCMVkm2....The sequence of pCMVkm2 is depicted in SEQ ID NO:2", which has 4328 base pairs.

3. Analysis

The Appellants assert that the plasmid DNA shown in Murphy, having over 4000 basepairs, would clearly not be considered an "oligonucleotide" by one skilled in the art. Dictionary definitions of the terms "oligonucleotide" and "oligomer" taken from scientific reference works include the following:

Oligonucleotide: A short sequence of nucleotides.[1]

Oligomer: General term for a short polymer most commonly consisting of amino acids (oligopeptides), nucleic acids (oligonucleotides), or sugars (oligosaccharides).[2]

Keeping in mind the standard that a claim term is to be given its broadest reasonable construction during prosecution, Appellants nonetheless assert that expanding the scope of the term "oligonucleotide" to include a 4328-base pair plasmid DNA would not be considered reasonable by one skilled in the art.

Accordingly, the reference does not show the claimed step of (i) "contacting each peptoid in the library with an oligonucleotide". Thus, Murphy cannot be said to anticipate the invention, and Appellants urge the Board to reverse the Examiner's rejection under 35 U.S.C. §102(b).

---

[1] S.T. Nicholl, *An Introduction to Genetic Engineering*, Cambridge University Press, 1994.

[2] H. Lodish *et al.*, *Molecular Cell Biology*, 3rd ed., Scientific American Books, Inc., New York, NY 1998.

ANALYSIS OF THE REJECTIONS UNDER 35 U.S.C. §103

Claims 13-17, 21 and 24-29 stand rejected under 35 U.S.C. §103(a) as being obvious over Murphy *et al.*, above, in view of Fasbender *et al.* (U.S. Patent No. 5,935,936).

1. The Examiner's Position and Appellants' Response: Murphy reference taken alone

The Murphy reference is described above. As discussed above, it does not show delivery or transfection of oligonucleotides.

In the Final Office Action, the Examiner stated that "one would have been motivated to use an oligonucleotide" by the teachings of Murphy "since Murphy discloses that this long chain polynucleotide are subject to degradation on delivery to the target site" (Final Office Action, dated September 23, 2003, page 7). The Appellants disagree with this conclusion, since this perceived problem (i.e. degradation of polynucleotides) would in fact motivate the skilled person to find ways of preventing degradation of the long chain polynucleotides, which is what the Murphy disclosure claims to do.

The Examiner then states that "One skilled in the art knows that these polynucleotides are normally condensed into its oligonucleotide to protect it from enzyme degradation". The Appellants do not see the logic in this statement, since a polynucleotide which is "protected from enzyme degradation" would more likely be prevented from forming "oligonucleotides".

The Examiner then states that "Murphy discloses that the peptoids condenses the polynucleotide to a smaller size. In such condensation and degradation [sic], the DNA may have been converted to its smaller fragments...This would be at least suggestive of the claimed oligonucleotides" (Final Office action, dated September 23, 2003, page 8).

The Examiner seems to suggest that "degradation" is implied by the term "condensation". Appellants observe that "condensing the polynucleotide to a smaller size" in fact refers to condensing the DNA molecule to a smaller physical size, not to shorter lengths ("Condensation of DNA by cationic polymers...has been shown to protect supercoiled DNA from degradation", page 1519, column 1; "the most effective transfection reagent... condensed DNA into highly homogenous spherical particles whose diameters were around 50-60 nm"; page 1520, column 2).

Since a primary motivation in Murphy *et al.* is protection of long chain polynucleotides from degradation, any occurrence of "oligonucleotides" would be something to be avoided. The

reference is therefore not "suggestive of oligonucleotides".

2. The Examiner's Position and Appellants' Response: Murphy in view of Fasbender

2(a). The Reference Teaching

Fasbender describes compositions useful for delivery of "therapeutically active molecules". The composition is a dispersion of a cationic amphiphile and a neutral co-lipid. (See, for example, the Abstract.) The cationic amphiphile is typically a conjugate of cholesterol with an aliphatic polyamine such as spermine (column 4, lines 65-67, and following).

The working examples in Fasbender describe the delivery of protein-encoding DNA, generally in the form of plasmids having hundreds or thousands of basepairs (see e.g. column 34, line 6; column 35, line 54; column 36, line 64-65; column 39, line 18; column 41, line 55; column 42, line 35; column 44, lines 8, 28, and 46; and Example 4, "Construction of Vectors"). There is no demonstration of delivery or transfection of oligonucleotides in the reference.

2(b). Analysis

(i.) The Examiner's Position

With regard to claim 26, which was not included in the rejection under §102(b), the Examiner notes that "Murphy does not disclose the lipid steroid...attached to the peptoid". The Examiner cites Fasbender as allegedly providing the missing disclosure: "Fasbender *et al.* discloses...cationic amphiphiles containing steroid, as the commonly known DC-chol" (page 7 of Office Action).

(ii.) Appellants' Response

Firstly, Fasbender does not disclose peptoid-lipid conjugates. The "cationic amphiphiles" employed in Fasbender, as noted above, are typically derived from polyamides such as spermine, not from peptoids.

Moreover, Fasbender characterizes the "cationic amphiphiles" noted by the Examiner, such as DC-chol, as having "*only modest activity*" in delivery of molecules into cells and providing uptake efficiencies which are "*insufficient* to support numerous therapeutic applications" (column 3, lines 6-9 and 27-35; emphasis added).

Fasbender addresses this insufficiency by employing, for transfection, a mixture of a cationic amphiphile with a separate co-lipid, typically a phospholipid (column 4, lines 11-63).

Accordingly, the reference teaches away from the use of "cationic amphiphiles containing steroid", or any other steroid conjugates, as delivery vehicles, in the absence of a separate co-lipid. (A reference should be considered as a whole, and portions arguing against or teaching away from the claimed invention must be considered. *Bausch & Lomb v. Barnes-Hind / Hydrocurve*, 796 F.2d 443, 230 USPQ 416, Fed. Cir. 1986.)

Accordingly, even if the teachings of these references were to be combined, the combined teachings would suggest, not the current invention, but rather the use of a cationic amphiphilic molecule as disclosed in Murphy, in combination with a co-lipid as disclosed in Fasbender, for use in delivery of polynucleotides. Neither reference, alone or in combination, teaches or suggests the screening of peptoids for transfection of oligonucleotides.

Accordingly, Appellants submit that the appealed claims 41-46 patentably define over the teachings of Murphy and Fasbender and ask that the Examiner's rejection under 35 U.S.C. §103(a) be reversed.

CONCLUSIONS

In view of the foregoing discussion, Appellants submit that the pending claims are in condition for allowance and patentably define over the prior art, and urge the Board to overturn the Examiner's rejections.

Respectfully submitted,

LeeAnn Gorthey
Reg. No. 37,337

Date: June 23, 2004

Correspondence Address:
Chiron Corporation
4560 Horton Street
Emeryville, CA 94608-2916

APPENDIX A: CLAIMS ON APPEAL

13. A method of identifying peptoids, in a library of different-sequence peptoids, which are effective in transfecting a cell with an oligonucleotide, the method comprising:

(i) contacting each peptoid in the library with an oligonucleotide, to form a plurality of peptoid-oligonucleotide mixtures,

(ii) contacting each said mixture with a cell;

(iii) screening each cell for transfection of the oligonucleotide, to identify transfected cells; and

(iv) identifying transfecting peptoids in mixtures contacted with transfected cells.

14. The method of claim 13, wherein said library of peptoids is provided in an array of physically separated compartments.

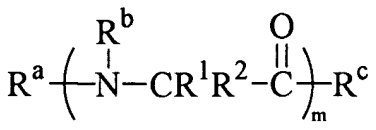
15. The method of claim 14, wherein said peptoids are supported on solid particles.

16. The method of claim 15, further comprising the step of releasing the peptoids from the particles in said compartments, prior to said contacting step (i).

17. The method of claim 15, wherein each compartment contains a single particle, and each particle contains a single peptoid.

21. The method of claim 13, wherein, in step (ii), each said mixture is contacted with a plurality of distinct cell types.

24. The method of claim 13, wherein said different-sequence peptoids have the general formula **I**:



I

where

R^a is selected from the group consisting of alkyl, aryl, aralkyl, aralkenyl, and aralkynyl, any of which may be substituted with one or more groups X; hydrogen, -OH, -SH, -COOH, sulfonyl, and a lipid moiety, wherein said lipid moiety may be conjugated to a linker moiety,

each R^b is independently selected from the group consisting of alkyl, aryl, aralkyl, aralkenyl, and aralkynyl, any of which may be substituted with one or more groups X; and hydrogen,

wherein at least one group R^b is not hydrogen;

R^c is selected from the group consisting of alkyl, aryl, aralkyl, aralkenyl, and aralkynyl, any of which may be substituted one or more groups X; hydrogen, -OH, -SH, $-NH_2$, -NHR, -NH(C=O)R, where R is lower alkyl; sulfonyl, hydrazine, and a lipid moiety, wherein said lipid moiety may be conjugated to a linker moiety;

X is selected from hydroxy, alkoxy, amino, guanidino, amidino, alkylamino, alkylthio, halogen, nitro, cyano, keto, aldehyde, carboxylic acid, carboxylic ester, carboxylic amide, sulfonic acid and sulfonic ester;

R^1 and R^2 are independently selected from hydrogen, lower alkyl, and lower alkoxy; and

m is an integer selected from 2 to about 50.

25. The method of claim 24, wherein in formula **I**, R^a comprises a lipid moiety, and R^c is selected from $-NH_2$, -NHR, and -NH(C=O)R, where R is lower alkyl.

26. The method of claim 25, wherein said lipid moiety is a sterol.

27. The method of claim 24, wherein in formula **I**, each of R^1 and R^2 is hydrogen.

28. The method of claim 24, wherein in formula **I**, at least one R^b includes a group which is cationic at physiologically relevant pH, and at least one R^b is uncharged at physiologically relevant pH.

29. The method of claim 28, wherein said cationic group is selected from aminoalkyl, guanidino, amidino, imidazole, and pyridinium.